

## GUEST EDITORIAL

# Limits of Resection for Ductal Carcinoma In Situ

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### INTRODUCTION

Ductal carcinoma in situ (DCIS) of the breast is a frustrating and confusing disease from a number of aspects. It is a new disease that has primarily been identified by mammography and defined without a large enough untreated control group to be certain of the natural history. Since the natural history is unknown, the need for treatment or the benefits of prophylaxis in any given patient are unclear. The extent of disease is not well defined by mammography and cannot be identified by palpation or gross inspection by the surgeon. Intraoperative decision making is limited by the difficulty of distinguishing DCIS from more benign conditions by frozen section and no satisfactory alternatives to frozen section have been widely validated. Although mastectomy is nearly completely protective [1], the irony of performing a mastectomy for a premalignant condition when breast conservation is routinely performed for invasive cancer is not lost on many patients. Enough patients have been treated with partial mastectomy with or without radiation therapy to establish the degree of safety of breast conservation in terms of the risk of in-breast recurrence and to provide some guidelines for the extent of resection. A discussion of the extent of resection in a partial mastectomy assumes that the surgeon will make a good-faith effort to avoid total mastectomy except in those cases where the resection that is required to obtain disease-free margins is so extensive that a mastectomy and reconstruction offer a better cosmetic result.

### MULTIFOCALITY VERSUS MULTICENTRICITY: IS DCIS LIMITED TO ONE AREA OF THE BREAST?

Multicentricity refers to disease occurring in more than one breast segment. Unicentric disease is limited to one breast segment. Unicentric, unifocal disease involves one area of one duct within a segment. Breast segments are not well defined by either the surgeon or the pathologist and histologic sections through a diseased area of the breast may transect involved ducts as they course in and

out of the plane of sectioning. Unifocal disease may appear to be multifocal because of the limited number of sections that it is practical to cut from a small piece of breast tissue. An accurate distinction between multifocal and multicentric disease is obviously more difficult and requires detailed examination of a whole breast. Because breast segments cannot be readily identified, multicentricity is usually defined by disease in non-contiguous quadrants. Probably the best analysis of this problem came from the studies of Holland et al. [2], who used the serial subgross technique of Eagen [3] to analyze multiple sections of whole breast specimens in order to define the extent of disease. X-rays were taken of multiple sections of whole breast specimens and areas that appeared to be suspicious radiographically were studied microscopically. In their analysis of 82 mastectomy specimens, Holland et al. [2] could find multicentric disease in only one case. In half of the cases studied, the diameter of the DCIS-involved tissue was larger than 5 cm and 34% involved more than one quadrant or were centrally located. These studies indicate that DCIS is almost invariably limited to one area of the breast and, therefore it is theoretically possible to remove DCIS completely without performing a mastectomy in the majority of patients. How often and in what circumstances DCIS can be excised with a satisfactory cosmetic result and with a low risk of subsequently developing invasive cancer are more complicated questions. The difficulty of achieving complete local excision by a resection that was more limited and more cosmetic than a true quadrantectomy was emphasized by Silverstein et al. [4]. In that series of 181 patients who had wide local excision as a biopsy, residual DCIS was found in 66% of mastectomy or reexcision specimens.

One implication of the belief that DCIS is a unicentric or segmental disease of one duct is that the disease can

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track toward the nipple [2,5]. The analysis of Holland et al. [2] showed that the nipple and main subareolar ducts were more likely to be involved when the disease was centrally located or larger than 4 cm. A tendency to track toward the nipple should be taken into consideration in planning excisions.

### RELATIONSHIP OF DCIS TO THE EXTENT OF MICROCALCIFICATIONS

DCIS is commonly discovered because a screening mammogram shows suspicious microcalcifications. The microcalcifications are then either removed with a needle-localized open biopsy or sampled with a stereotactically directed core needle biopsy. Unfortunately, the microcalcifications rarely define the extent of disease. To a limited degree, the type or grade of DCIS can be predicted from the mammographic appearance. High-grade "comedo" type DCIS tends to be associated with branching type microcalcifications, whereas low-grade forms tend to be associated with small irregular type microcalcifications [2]. The extent of disease can only be predicted to a limited degree for either type. In their initial studies correlating the extent of disease with the distribution of microcalcifications on a routine, unmagnified mammogram, Holland et al. [2] found that DCIS extended 2 cm or less away from the index microcalcifications in 80% of the cases of high-grade DCIS and 54% of the cases of low-grade DCIS. That is, a margin 2 cm away from the microcalcifications seen on mammogram would have cleared all of the high-grade DCIS in 80% of the cases. A 2 cm margin would have cleared the low-grade DCIS only 54% of the time. Magnification views can demonstrate microcalcifications that are not seen on routine mammographic views. In a subsequent study, Holland and Hendriks [6] correlated the extent of DCIS by the serial subgross technique with microcalcifications seen on magnified mammographic views. The correlation with high-grade lesions remained at about 80% for a 2 cm margin. However, a 2 cm margin would have cleared approximately 75% of low- and intermediate-grade lesions, a 20% (absolute) improvement over the results with standard mammograms. These data suggest that at least 20% of the time a wide margin (2 cm margin around an index cluster of microcalcifications seen on magnified views) will fail to clear all of the DCIS. That 20% figure probably represents an irreducible minimum number of patients who will require a major, deforming, partial mastectomy or a total mastectomy to clear the DCIS. These data also suggest that magnification views after presumed complete excision may be helpful in identifying patients with residual disease who need reexcision.

### WHAT SIZE PATHOLOGIC MARGIN IS ACCEPTABLE?

In theory, a small area of microcalcifications resected with a wide, negative pathologic margin should have a relatively low risk of recurrence. Unfortunately, the unknown or variable margins and the short follow-up reported in many series make the interpretation of results difficult. Furthermore, all margins may not be equal in portent. DCIS approaching a superficial margin beneath the skin or a deep margin when the pectoral fascia is in the specimen may not have the same implications as margins bordered by breast tissue.

In general, recurrence rates after wide excision alone without radiation therapy have been high enough to cause concern and to make radiation therapy advisable at least for high-grade lesions. Without radiation therapy, recurrence rates have been in the 15–20% range [4,7–11]. Radiation therapy appears to reduce the risk of recurrence by about 50% [9]. Even if radiation therapy is used, margins appear to make a difference. In the NSABP-B17 protocol, patients with "uncertain or involved" margins had a more than 2-fold increase in the rate of in-breast recurrences compared to patients with "free" margins even after radiation therapy. [10].

The definition of clear or involved margins has varied with different authors. Silverstein et al. [12] used "10 mm or greater" as a definition of "widely clear, tumor-free margins." Such a wide margin was usually achieved by reexcision with no residual DCIS or only focal residual DCIS in the biopsy cavity. With "widely clear, tumor-free margins" the risk of in-breast tumor recurrence was low. If a "clear margin" was defined as tumor 1 mm or more from the inked margin, Silverstein et al. [4] found residual DCIS in 43% of patients initially declared to be "clear" but subjected to reexcision or mastectomy.

Solin et al. [13] used a 3-step definition of margins. The margin was scored as "negative" if all tumor was more than 2 mm from the inked margin. The margin was scored as "positive" when tumor was identified at the inked margin and was "close" when tumor was identified 2 mm or less but not at the inked margin. Using that definition, 5% of patients with negative margins had local recurrences with 8 years of follow-up compared to a 10% local recurrence rate in patients with positive or close margins. In a subsequent publication, results at 10 years were 10% in-breast recurrence for negative margins and 17% for positive or close margins [14]. Unfortunately, a large number of patients (47%) had unknown margins and, possibly because of small numbers, there was no statistically significant correlation with margin ( $P = 0.16$ ).

In a retrospective analysis, Silverstein et al. [12] found that tumor size, margin width, and pathologic classifica-

tion were statistically significant predictors of the likelihood of breast recurrence after breast conserving surgery for DCIS. Margins were divided into 3 categories: clear tumor margins of 10 mm or more, intermediate margins of 1–9 mm, and margins less than 1 mm. Margins of more than 10 mm were mostly commonly achieved by reexcision and finding no residual DCIS or minimal DCIS in the biopsy cavity. The authors combined the 3 prognostic indicators into an index which, if it can be validated prospectively, may be helpful for predicting those patients who need radiation therapy or possibly even mastectomy. The basic idea that recurrence is related not just to margins but to histology and tumor size is important. Studies to validate this concept and to quantify the elements of the index will be interesting.

Another note of caution should be sounded with regard to the interpretation of margins. The report of a margin distance is the result of a specific process of tissue preparation and analysis which may differ among pathologists and from one institution to another. General recommendations for tissue processing were agreed upon at a recent consensus conference [15], but the number of slides per specimen or the number of slides per unit volume of a specimen may be markedly different in different institutions. The cost of slide preparation is an important factor limiting tissue analysis. One might anticipate that the more slides that are prepared the better the margin analysis and the more accurate the prognostic groupings. In other words, if methods of tissue preparation and analysis are different, one institution's "10 mm margins" will be different from another's.

In summary, the limits of resection for DCIS are not well defined. By targeting a 2 cm breast margin around the microcalcifications seen on a magnification view mammogram, the disease should be cleared by the resection specimen approximately 80% of the time. Unless the area of microcalcification is quite small, resection of the index area and a 2 cm margin will be the equivalent of a quadrant or at least will result in a cosmetic deformity. For the 20% of patients who have disease at the margins of a wide excision or a quadrantectomy, reexcision may be possible or the best cosmetic result may be obtained by mastectomy and reconstruction.

The definition of a "clear margin" is controversial

and operational. A 2 mm border of microscopically clear breast tissue around the area of DCIS results in a relatively low risk of in-breast recurrence in patients who receive breast irradiation after excision. Selection of patients who can safely avoid radiation will probably involve some combination of criteria including tumor grade, size, and margin width.

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